PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 570708020WO0	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US04/43249	International filing date *(day/month/year)* 20 December 2004 (20.12.2004)	Priority date *(day/month/year)* 24 December 2003 (24.12.2003)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/365; C07D 493/22 and US Cl.: 514/468; 549/297		
Applicant PHARMAGENESIS, INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 24 October 2005 (24.10.2005)	Date of completion of this report 13 December 2005 (13.12.2005)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Bernard Dentz Telephone No. 571 272-1600

Form PCT/IPEA/409 (cover sheet)(April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/43249

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into English, which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))
- ☐ publication of the international application (under Rule 12.4(a))
- ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:
pages 1-29 as originally filed/furnished
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☒ the claims:
pages 30-34 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* 35 received by this Authority on 24 October 2005 (24.10.2005)
pages* NONE received by this Authority on

☒ the drawings:
pages as originally filed/furnished
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 27-30

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 27-30

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 7,8,11-15, 20 and 25	YES
	Claims 1-6,9,10,16-19,21-24 and 26	NO
Inventive Step (IS)	Claims 7,8,11-15 and 20	YES
	Claims 1-6, 9, 10,16-19 and 21-26	NO
Industrial Applicability (IA)	Claims 1-26	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-6, 9,10,16-18, 21-24 and 26 lack novelty under PCT Article 33(2) as being anticipated by Ning et al. It discloses the biotransformation of triptolide to 5-alpha-hydroxytriptolide. See pages 4209 and 4210. It discloses that it can be used to effect apoptosis in a cell. See p. 4209, col.1 and p. 4211, col. 2, last paragraph to p. 4212, col. 1, first complete paragraph.

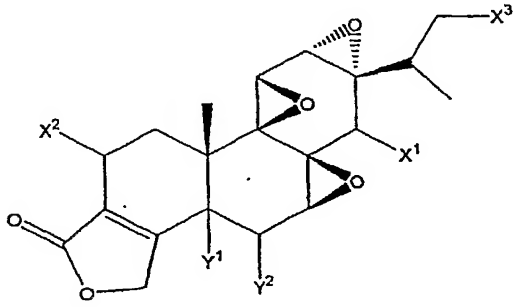
Claims 1-6, 9,10, 16-18 and 21-26 lack an inventive step under PCT Article 33(3) as being obvious over Ning et al. Claim 25 is drawn to a method of effecting immunosuppression in a subject in need therefore. The article begins by stating that the herb Tripterygium wilfordii Hook.f, Lei Gong Teng in Chinese, was used in traditional Chinese medicine for the treatment of various diseases including systemic lupus erythematous and rheumatoid arthritis, which are known to be autoimmune diseases. It then states that triptolide, isolated therefrom in 1972, has been shown to be effective in the treatment of autoimmune diseases and to have potent antileukemic and antitumor activities.

It goes on to state that the application of triptolide in pharmacy is limited by its strong toxicity. To find more effective compounds with less toxicity, structural modifications of triptolide and its analogues has been carried out. Thus in the work described in the article a single hydroxyl group is attached at various positions of triptolide by treating it with a microorganism. 5alpha-hydroxytriptolide, a compound embraced by compound claims 1-6, 9, 10, 16-18 and 21-24, was one of the compounds obtained. It was found to have in vitro cytotoxic activities against human tumor cell lines. In view of that fact that it shares that activity with its parent triptolide, it would be expected that it would also share its utility in treating autoimmune diseases. Thus claim 25 lacks an inventive step.

Claims 7,8, 11-15, 19 and 20 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest those triptolide derivatives.

Claims 1-26 meet the criteria set out in PCT Article 33(4), and thus possess industrial applicability because the subject matter claimed can be made or used in industry.

27. A method of preparing a 5-hydroxy triptolide compound of formula I



I

where

X^1 is OR^1, where R^1 is selected from hydrogen, $C(=O)R^2$, and $C(=O)OR^2$, where R^2 is selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, and acyloxyalkyl;

X^2 and X^3 are independently OR^1 or hydrogen, at least one of X^2 and X^3 being hydrogen;

Y^1 = OH; and Y^2 = H;

by reaction of a starting triptolide compound of formula I in which X^1, X^2 and X^3 are as defined above, Y^1 = H, and Y^2 = H, with selenium dioxide.

28. The method of claim 27, wherein R^1 is selected from hydrogen and $C(=O)R^2$, and R^2 is selected from lower alkyl, phenyl, and benzyl.

29. The method of claim 28, where R^1 is hydrogen.

30 The method of claim 29, wherein each of X^2 and X^3 is hydrogen, and said 5-hydroxy triptolide compound is 5α-hydroxytriptolide.